Inferior control of low-density lipoprotein cholesterol in women is the primary sex difference in modifiable cardiovascular risk: A large-scale, cross-sectional study in primary care

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Abstract: BACKGROUND AND AIMS Sex differences in cardiovascular prevention have been reported, yet the role of sex with regard to different modifiable risk factors such as low-density lipoprotein cholesterol (LDL-C), systolic blood pressure (BP), and glycated hemoglobin (HbA1c) in primary care settings is unclear. Therefore, we studied sex differences in assessment and measured values of LDL-C, BP, and HbA1c in primary and secondary cardiovascular prevention delivered by general practitioners. METHODS This cross-sectional study was based on electronic medical records of 59,092 primary care patients (51.9% women) aged 40-79 years in Switzerland. Multilevel regression was used to model associations of sex with assessment and measured values of LDL-C, BP, and HbA1c in 2018. RESULTS In both primary and secondary prevention, women had lower LDL-C assessment rates (age-adjusted odds ratio (aOR) 0.71 [95% confidence interval (CI) 0.67 to 0.75] and 0.70 [CI 0.51 to 0.95]), and higher measured LDL-C values than men (age-adjusted difference 0.30 mmol/L [CI 0.25 to 0.35] and 0.28 mmol/L [CI 0.07 to 0.48]). Compared with men, women in primary prevention displayed lower BP and HbA1c assessment frequencies (aOR 0.77 [CI 0.73 to 0.81] and 0.76 [CI 0.71 to 0.80]) and measured values (age-adjusted difference -2.49 mmHg [CI -2.99 to -1.79] and -0.19% [CI -0.24 to -0.14]), while there was no sex difference in secondary prevention. Age-dependent increases in measured values of LDL-C, BP, and HbA1c were greater in women than men. CONCLUSIONS Control of LDL-C in women in primary care should be improved to reduce sex-based inequalities in prevention of cardiovascular disease.

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Inferior control of low-density lipoprotein cholesterol in women is the primary sex difference in modifiable cardiovascular risk: A large-scale, cross-sectional study in primary care

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ABSTRACT

Background and aims: Sex differences in cardiovascular prevention have been reported, yet the role of sex with regard to different modifiable risk factors such as low-density lipoprotein cholesterol (LDL-C), systolic blood pressure (BP), and glycated hemoglobin (HbA1c) in primary care settings is unclear. Therefore, we studied sex differences in assessment and measured values of LDL-C, BP, and HbA1c in primary and secondary cardiovascular prevention delivered by general practitioners.

Methods: This cross-sectional study was based on electronic medical records of 59,092 primary care patients (51.9% women) aged 40–79 years in Switzerland. Multilevel regression was used to model associations of sex with assessment and measured values of LDL-C, BP, and HbA1c in 2018.

Results: In both primary and secondary prevention, women had lower LDL-C assessment rates (age-adjusted odds ratio (aOR) 0.71 [95% confidence interval (CI) 0.67 to 0.75] and 0.70 [CI 0.51 to 0.95]), and higher measured LDL-C values than men (age-adjusted difference 0.30 mmol/L [CI 0.25 to 0.35] and 0.28 mmol/L [CI 0.07 to 0.48]). Compared with men, women in primary prevention displayed lower BP and HbA1c assessment frequencies (aOR 0.77 [CI 0.73 to 0.81] and 0.76 [CI 0.71 to 0.80]) and measured values (age-adjusted difference -2.49 mmHg [CI -2.99 to -1.79] and -0.19% [CI -0.24 to -0.14]), while there was no sex difference in secondary prevention. Age-dependent increases in measured values of LDL-C, BP, and HbA1c were greater in women than men.

Conclusions: Control of LDL-C in women in primary care should be improved to reduce sex-based inequalities in prevention of cardiovascular disease.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death and loss of quality-adjusted life years in women and men alike [1,2]. Cardiovascular risk is driven by both non-modifiable risk factors, particularly age [3], as well as modifiable risk factors, some being amenable to pharmacologic therapy, such as elevated low-density lipoprotein cholesterol (LDL-C), blood pressure (BP), and glycated hemoglobin (HbA1c) [4]. Interestingly, age differently affects CVD development in women and men: before menopause, women are largely protected from CVD because of the cholesterol-lowering, vasodilator, anti-inflammatory, and anti-diabetic effects of endogenous estrogens [5]. After menopause, the prevalence of modifiable risk factors increases, which may explain why women develop CVD about 8 years later in life than men [6].

CVD prevention strategies, including assessment and treatment of modifiable risk factors, are equally effective in women and men in reducing cardiovascular morbidity and mortality [7–9]. However, women in both primary prevention (i.e., patients considered at risk for CVD) and secondary prevention (i.e., patients with established CVD) are less likely than men to have individual cardiovascular risk factors assessed [10–12]. Moreover, some studies indicated that fewer women received appropriate preventive medications and achieved target values for LDL-C, systolic BP, or HbA1c than men [10,11,13,14], while others found no differences [15]. However, many previous investigations did

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not study patients in both primary and secondary prevention [11,13], derived data from randomized trials [10] or were otherwise not based on primary care settings [12], and there is only limited information on European patients currently available. Moreover, it is unclear whether sex differences disproportionately apply to distinct modifiable risk factors, which may have important implications for improving cardiovascular care. Therefore, we used a large Swiss primary care cohort to compare age-dependent differences between women and men in assessment, measured values and treatment of LDL-C, BP, and HbA1c in contemporary primary and secondary prevention of CVD.

2. Patients and methods

2.1. Design, setting and participants

This retrospective, cross-sectional study is based on electronic medical records provided by the Family Medicine International Classification of Primary Care Research using Electronic Medical Records (FIRE) project, which has been described previously [16]. Briefly, the FIRE database collects data from electronic medical records of currently over 500 general practitioners in Switzerland. Records contain patient demographics, laboratory measurements, vital signs, drug prescriptions and diagnosis codes based on the 2nd edition of the International Classification of Primary Care (ICPC-2) [17].

We extracted information of patients aged 40–79 years with at least two consultations, one before 2017 and one during 2018, to ensure that sufficient baseline data was available to study preventive measures. We retrieved information on age, sex, CVD history, cardiovascular risk category [18,19] (Supplementary Table 1), the number of consultations, the number of LDL-C, BP, and HbA1c measurements, as well as the latest recorded values of LDL-C, high-density lipoprotein cholesterol (HDL-C), total cholesterol, triglycerides, systolic BP, diastolic BP, and HbA1c in 2018. We also extracted drug prescriptions for the treatment of dyslipidemia, hypertension, and diabetes [20] (Supplementary Table 2). For statins, we retrieved daily doses of the latest prescription in 2018 and calculated the treatment intensity [21]. Based on absence or presence of a CVD history, patients were classified into primary or secondary prevention (Supplementary Table 3 and Supplementary Figure 1). Patients with a first CVD diagnosis in 2018 were excluded to avoid confounding of the primary and secondary prevention groups.

Data acquisition and analyses have been approved by the local ethics committee (BASEC-Nr. Req-2017-00797) and are in accordance with the World Medical Association Declaration of Helsinki and with good clinical practice guidelines. The ethics committee waived the requirement to obtain patients' informed consent.

2.2. Statistical analyses

All statistical analyses were performed using R software version 3.4.0 [22]. To describe the data, we used counts and proportions (*n* and %) or medians with interquartile ranges. Group comparisons were carried out using Wilcoxon rank-sum tests, Chi-squared tests, or Poisson regression, as appropriate. We assumed significance for $p < 0.05$. To study assessment and measured values of LDL-C, BP, and HbA1c, respectively, we adopted multilevel regression models, accounting for the hierarchical structure of the data with patients being clustered within general practitioners. Assessment of LDL-C, BP, and HbA1c was modeled with logistic regression (assessed *vs.* not assessed), and linear regression was used to model the measured values. All regression analyses were carried out separately for patients in primary and secondary prevention. Preselected fixed effect variables were patient sex and age (centered, also as quadratic term), with interactions. For the LDL-C values of patients in primary prevention, we repeated the analysis with stratification for cardiovascular risk categories [18]. We added bootstrap 95% confidence intervals (CI) to predicted values, using the add_ci() function from the R package ciTools (2000 simulations, disregarding random effects). To translate estimated interaction coefficients into effect sizes with CIs and *p* values for multiple comparisons, we used the glht() function from the R package multcomp. Results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

3. Results

3.1. Study population

We studied 59,092 patients of 167 general practitioners from 62 practices: 95.9% ($n = 56{,}694$) in primary prevention and 4.1% ($n = 2{,}398$) in secondary prevention (Supplementary Figure 1). Patient characteristics of women and men in primary and secondary prevention are given in Table 1.

3.2. Assessment of LDL-C, BP, and HbA1c

In primary prevention, LDL-C, BP, and HbA1c were less frequently assessed in women than in men (age-adjusted odds ratio (aOR) 0.71 [95% CI 0.67 to 0.75], 0.77 [95% CI 0.73 to 0.81], and 0.76 [95% CI 0.71 to 0.81], respectively), but assessment proportions increased with age in both sexes. In secondary prevention, only LDL-C was less frequently assessed in women than in men (aOR 0.70 [95% CI 0.51 to 0.95]), and this was independent of age (Fig. 1, Table 1 and Supplementary Table 4). In contrast, BP and HbA1c assessment proportions in secondary prevention were not associated with sex but increased with age. With regard to concomitance of LDL-C, BP, and HbA1c assessments, men were more likely to have two or all three risk factors measured, whereas women were more likely to have only one or none of the risk factors assessed in both primary and secondary prevention (Table 1).

3.3. Measured values and treatment of LDL-C

3.3.1. Sex differences in values and treatment

LDL-C levels were higher in women than in men both in primary prevention (median 3.2 mmol/L *vs.* 3.0 mmol/L, age-adjusted difference 0.30 mmol/L [95% CI 0.25 to 0.35]) and secondary prevention (median 2.3 mmol/L *vs.* 2.0 mmol/L, age-adjusted difference 0.28 mmol/L [95% CI 0.07 to 0.48]) (Fig. 2A, Table 2 and Supplementary Table 5). The difference in primary prevention persisted when patients were stratified according to cardiovascular risk categories (Supplementary Figure 2 and Supplementary Table 5). Women in both primary and secondary prevention were less often treated with lipid-modifying drugs and received less high-intensity treatment than men (Table 2).

3.3.2. Age dependence of values

Age differently affected LDL-C levels by sex in primary prevention (Fig. 2A and Supplementary Table 5): In women, LDL-C levels increased until age 60 years and then decreased, whereas in men, LDL-C levels decreased roughly by 0.2 mmol/L per 10 years. The two curves intersected at approximately age 50 years, indicating that LDL-C levels were higher in women than in men older than 50 years (predicted difference 0.4 mmol/L at age 70 years, for instance). Age did not significantly affect LDL-C levels in secondary prevention, independent of sex.

3.4. Measured values and treatment of BP

3.4.1. Sex differences in values and treatment

Systolic BP was slightly lower in women than in men in primary prevention (median 131 mmHg *vs.* 134 mmHg, age-adjusted difference -2.34 mmHg [95% CI -2.99 to -1.79]) (Fig. 2B, Table 3 and Supplementary Table 5), while there was no significant age-adjusted sex difference in secondary prevention (median 136 mmHg *vs.* 134 mmHg). Similarly, women in primary but not in secondary prevention were less often treated with antihypertensive drugs (Table 3).

Table 1
Sex-dependent risk factor assessment in primary and secondary prevention.

	Primary prevention			Secondary prevention		
	Women	Men	*p* value	Women	Men	*p* value
n	29,967	26,727		696	1,702	
Age, years	57 (49–68)	57 (49–67)	0.442[a]	71 (63–76)	68 (60–74)	<0.001[a]
Cardiovascular risk category[b], %			<0.001[c]			N/A
Low-moderate	81.3	76.5		N/A	N/A	
High	10.6	10.5		N/A	N/A	
Very high	8.1	13.0		100	100	
Number of annual consultations	4 (2–9)	4 (2–8)	<0.001[d]	8 (4–14)	8 (4–13)	<0.001[d]
LDL-C assessment, %			<0.001[c]			0.001[c]
No measurement	77.2	71.8		55.5	46.5	
1 measurement	19.6	24.2		33.9	40.8	
≥2 measurements	3.1	4.0		10.6	12.7	
BP assessment, %			<0.001[c]			0.888[c]
No measurement	56.9	53.0		32.2	30.8	
1 measurement	25.4	27.7		26.1	25.8	
≥2 measurements	17.7	19.4		41.7	43.4	
HbA1c assessment, %			<0.001[c]			0.213[c]
No measurement	77.0	73.6		58.8	53.6	
1 measurement	15.3	16.5		21.8	23.0	
≥2 measurements	7.6	9.9		19.4	23.4	
Concomitant assessment of LDL-C, BP, and HbA1c, %			<0.001[c]			0.013[c]
All 3 assessed	10.2	14.6		26.4	30.8	
2 assessed	15.6	16.3		22.7	26.3	
1 assessed	27.0	25.3		28.9	24.0	
None assessed	47.2	43.8		22.0	18.9	

BP, blood pressure; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol.
[a] Data are median (interquartile range) and analyzed using the Wilcoxon rank-sum test.
[b] Cardiovascular risk was categorized as described [18,19], with very high risk indicating established cardiovascular disease, diabetes mellitus with target organ damage or an additional major risk factor, severe chronic kidney disease, or a Systematic Coronary Risk Estimation (SCORE) ≥10%; high risk indicating single risk factors (very high BP or cholesterol), or diabetes mellitus without risk factors or target damage, or moderate chronic kidney disease, or SCORE ≥5% and <10%; low-moderate risk indicating all remaining patients.
[c] Analyzed using Chi-squared test.
[d] Data are median (interquartile range) and analyzed using Poisson regression.

3.4.2. Age dependence of values

Systolic BP increased approximately linearly with age, with sex-dependent intercepts and slopes (Fig. 2B). In primary prevention, systolic BP in women was 121 mmHg at age 40 years (predicted) and increased by 5 mmHg per 10 years of age, whereas in men, it was 129 mmHg at age 40 years (predicted) and increased by 3 mmHg per 10 years of age (Supplementary Table 5). The two curves intersected at age 70–75 years. In secondary prevention, systolic BP in women was 125 mmHg at age 40 years (predicted) and increased by 4 mmHg per 10 years of age, whereas in men, it was 127 mmHg at age 40 years (predicted) and increased by 2 mmHg per 10 years of age (Supplementary Table 5).

3.5. Measured values and treatment of HbA1c

3.5.1. Sex differences in values and treatment

HbA1c values were slightly lower in women compared to men in primary prevention (median 5.6% *vs.* 5.7%, age-adjusted difference -0.19% [95% CI -0.24 to -0.14]) (Fig. 2C, Table 4 and Supplementary Table 5). In contrast, there was no age-adjusted sex difference in secondary prevention (median 5.9% *vs.* 6.0%). Similarly, women in primary but not in secondary prevention were less often treated with antidiabetic drugs (Table 4).

3.5.2. Age dependence of values

In primary prevention, HbA1c increased approximately linearly with age from 5.5% at age 40 years (predicted) by 0.14% per 10 years in women, and from 5.8% at age 40 years (predicted) by 0.09% per 10 years in men (Fig. 2C and Supplementary Table 5). In secondary prevention, HbA1c values were not associated with age.

4. Discussion

The majority of cardiovascular events can be prevented by targeting modifiable risk factors both in women and men [7–9]. Nevertheless, in this large contemporary cohort of about 60,000 primary care patients, we found that women had lower age-adjusted LDL-C assessment rates, higher LDL-C levels, and less intensive lipid-lowering treatment in both primary and secondary prevention. In contrast, assessment and values of BP and HbA1c were lower in women than men in primary prevention, while there was no difference in secondary prevention. These findings indicate that control of LDL-C in women is disproportionally inferior compared to other modifiable risk factors.

In our study, LDL-C values were considerably higher in women older than 50 years, even in patients at very high risk of cardiovascular events. In fact, LDL-C differed by 0.3 mmol/L overall and by 0.4 mmol/L at age 70 years in both primary and secondary prevention. This is concerning given that a 1 mmol/L reduction in LDL-C lowers the 5-year incidence of major cardiovascular events by approximately 20% in women and men alike [23,24]. In contrast to LDL-C, BP and HbA1c values were slightly lower in women than men in primary prevention and similar in secondary prevention. Accordingly, BP and HbA1c were less frequently assessed and treated in women than men in primary prevention, while there was no difference in secondary prevention. Interestingly, these findings from patients in primary prevention suggest that the overall risk of elevated systolic BP and HbA1c was lower in women than men aged 40–79 years, even though it increased more profoundly with age in women. In contrast to LDL-C, the patients' sex played no major role in the general practitioners' decision to assess and control BP and HbA1c in secondary prevention. Overall, whereas BP and HbA1c were well controlled, LDL-C levels were above recommended treatment goals in secondary prevention [8,9]. Our findings are supported by studies indicating inferior control of LDL-C [12–14,25] as well as by

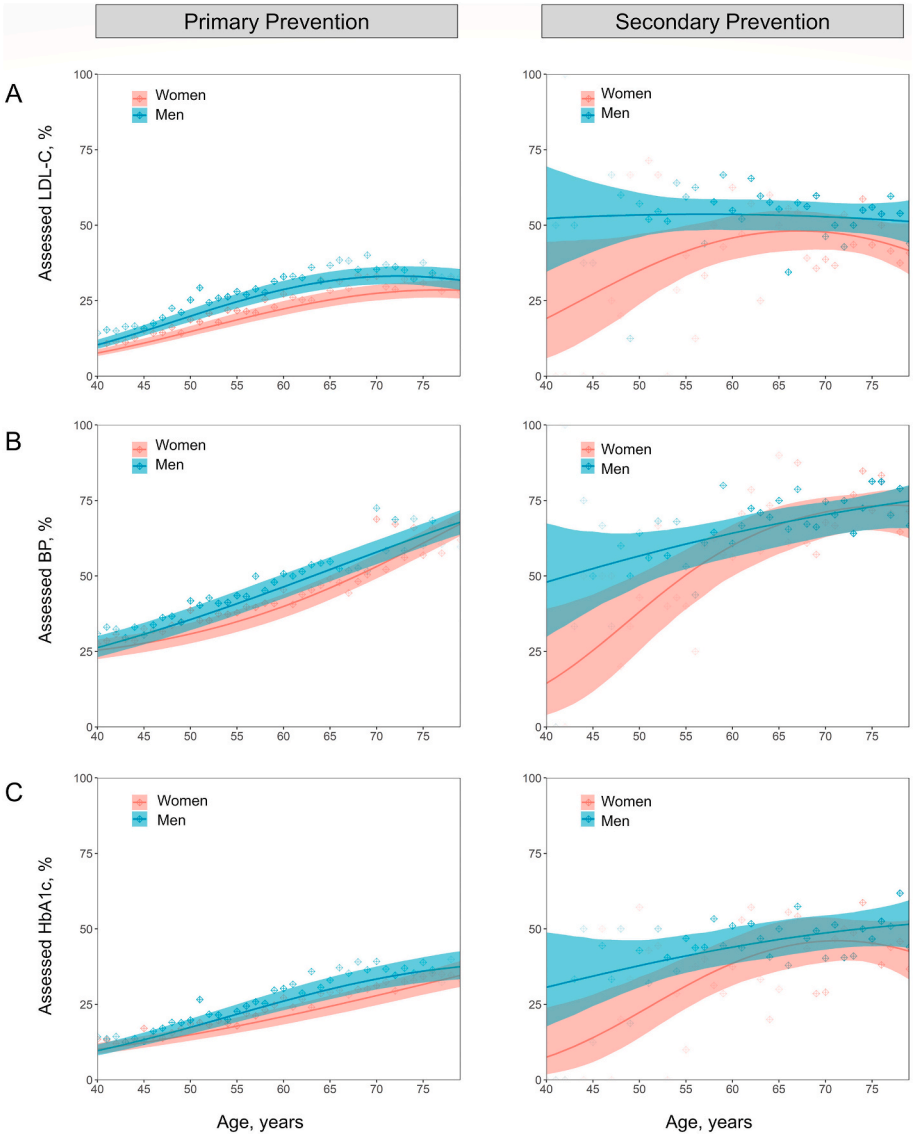

Fig. 1. Sex- and age-dependent risk factor assessment in primary and secondary prevention.
Predicted (continuous line with 95% confidence intervals) and empirical (diamonds) proportions of LDL-C (A), BP (B), and HbA1c (C) assessments in women (red) and men (blue) per patient year. Transparency of diamonds indicates the number of patients (maximum to minimum with increasing transparency). BP, blood pressure; HbA1c; glycated hemoglobin; LDL-C; low-density lipoprotein cholesterol. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

observations of equal or even better control of BP and HbA1c [11,12,15,26] in women compared to men.

It has previously been reported that women with CVD had higher LDL-C levels but were less likely to receive statin therapy than men [13,14], and lower statin prescription rates in women compared to men in secondary prevention (77.7% *vs.* 82.8%) have recently been confirmed in the European Society of Cardiology EUROASPIRE V registry [27]. Similarly, observational data collected in the United States showed that women eligible for statin therapy for both primary or secondary prevention were less likely than men to be offered treatment [28] and to receive guideline-recommended statin intensity [25,29]. The differences in preventive measures targeting LDL-C between women and men could have several reasons. First, general practitioners may unconsciously and biasedly perceive women to be at lower risk of CVD and thus at lower need for preventive measures [14,30]. Second, female sex is a risk factor for statin-associated adverse drug reactions such as muscle symptoms and new-onset diabetes [31], which may prompt physicians to a less frequent assessment and less intensive treatment as observed in our study. However, we also found that nonstatin therapies such as ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors were less frequently used in women compared with men, although the opposite would be expected if adverse effects of statins were the main driver of their less frequent prescription. Third, women were less frequently studied in clinical trials on statins, leading to an evidence gap [32]. However, data from randomized trials on intensive statin therapy clearly indicate that women and men derive equal reductions in the risk of cardiovascular events [33,34]. Similarly, a large meta-analysis of 27 clinical studies (46,675 women and 127,474 men) showed that the proportional reductions in major cardiovascular events per 1.0 mmol/L decrease in LDL-C were similar for women and men, as were reductions in all-cause mortality with statin therapy [24].

The present study adds several novel findings on sex inequalities in both screening and treatment of modifiable cardiovascular risk. First, our conclusion on disproportionately inferior LDL-C control in women is based on age-dependent assessment rates and measured values of the three major cardiovascular risk factors amenable to pharmacologic therapy in primary as well as in secondary prevention, and thus more comprehensive than previous studies [10,11,13]. In fact, risk assessment in apparently healthy people (i.e., primary prevention) is relevant for cardiovascular outcomes but remains understudied particularly with regard to sex inequalities. Second, in contrast to previous observations [12,13], we only included patients seen by general practitioners, who are largely responsible for cardiovascular prevention in Switzerland. This study is the first to investigate sex differences in cardiovascular

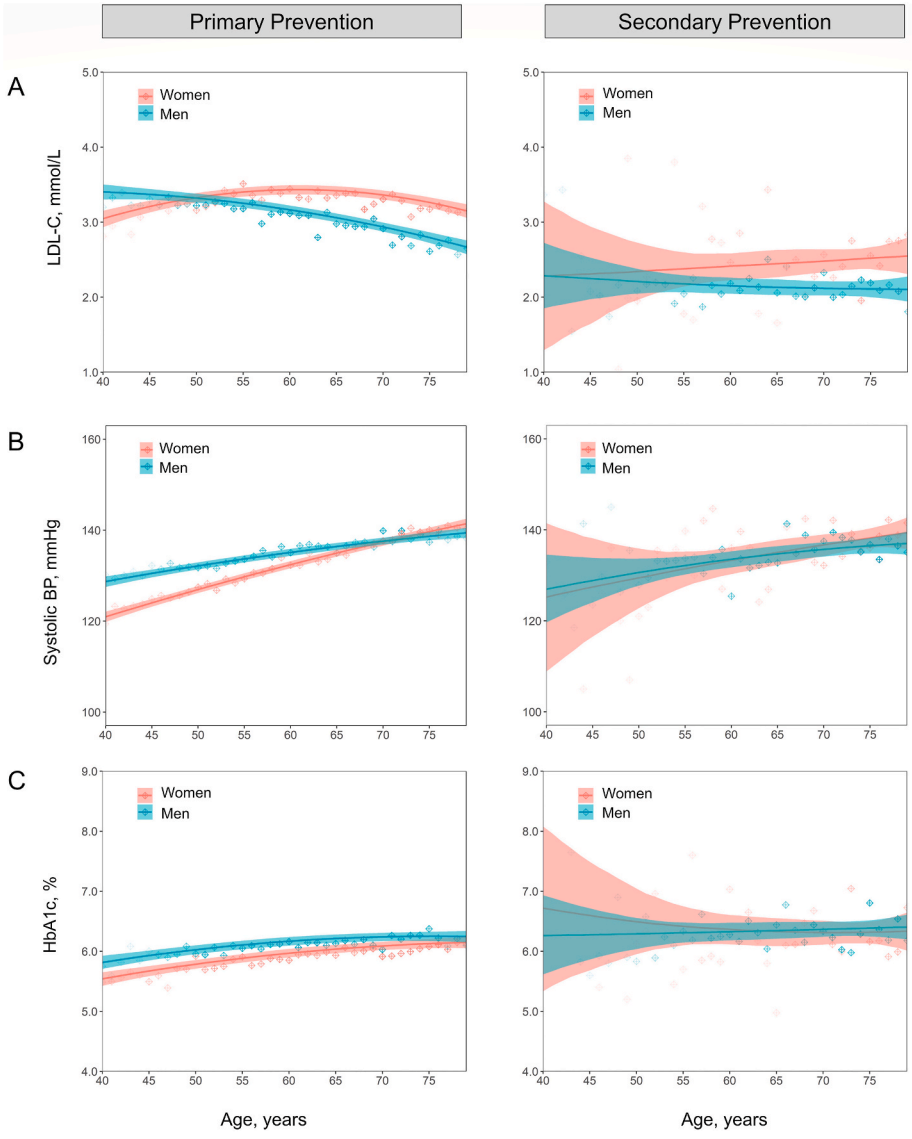

Fig. 2. Sex- and age-dependent measured risk factor values in primary and secondary prevention.
Predicted (continuous line with 95% confidence intervals) and empirical mean (diamonds) values for LDL-C (A), systolic BP (B), and HbA1c (C) in women (red) and men (blue) per patient year. Transparency of diamonds indicates the number of patients (maximum to minimum with increasing transparency). BP, blood pressure; HbA1c; glycated hemoglobin; LDL-C; low-density lipoprotein cholesterol. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Sex-dependent measured lipid values and lipid-modifying treatment in primary and secondary prevention.

	Primary prevention			Secondary prevention		
	Women	Men	*p* value	Women	Men	*p* value
n	5,562	6,120		264	762	
LDL-C, mmol/L	3.2 (2.5–3.9)	3.0 (2.3–3.7)	<0.001[a]	2.3 (1.7–3.1)	2.0 (1.6–2.6)	<0.001[a]
HDL-C, mmol/L	1.6 (1.3–1.9)	1.3 (1.0–1.5)	<0.001[a]	1.5 (1.3–1.8)	1.2 (1.0–1.5)	<0.001[a]
Non-HDL-C, mmol/L	3.8 (3.1–4.6)	3.7 (3–4.5)	<0.001[a]	2.9 (2.3–3.8)	2.7 (2.2–3.3)	<0.001[a]
Triglycerides, mmol/L	1.3 (0.9–1.9)	1.4 (1.0–2.1)	<0.001[a]	1.4 (0.9–1.9)	1.4 (1.0–2.0)	0.931[a]
Total cholesterol, mmol/L	5.5 (4.8–6.3)	5 (4.3–5.8)	<0.001[a]	4.6 (3.8–5.5)	3.9 (3.4–4.6)	<0.001[a]
Lipid-modifying treatment, %			<0.001[b]			0.018[b]
No treatment	69.9	63.5		15.2	9.2	
Low intensity statin	1.3	1.0		3.4	1.7	
Moderate intensity statin	18.1	18.8		32.6	30.1	
High intensity statin	6.9	12.5		43.9	53.3	
Statin of unknown intensity	2.7	2.7		4.5	3.7	
Ezetimibe	2.5	3.4		16.3	22.4	
PCSK9 inhibitor	0.05	0.02		1.14	1.18	

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.
[a] Data are median (interquartile range) and analyzed using the Wilcoxon rank-sum test.
[b] Analyzed using Chi-squared test.

Table 3
Sex-dependent measured BP values and antihypertensive treatment in primary and secondary prevention.

	Primary prevention			Secondary prevention		
	Women	Men	*p* value	Women	Men	*p* value
n	12,907	12,571		472	1,177	
Systolic BP, mmHg	131 (120–143)	134 (124–145)	<0.001[a]	136 (126–148)	134 (124–145)	0.044[a]
Diastolic BP, mmHg	80 (74–88)	82 (77–90)	<0.001[a]	80 (71–85)	80 (72–86)	0.024[a]
Antihypertensive treatment, %			<0.001[b]			0.111[b]
No treatment	54.4	50.5		12.3	12.7	
RAAS inhibitor	41.6	46.8		84.3	84.4	
Beta blocker	19.9	18.9		56.8	61.3	
Calcium channel blocker	13.2	13.0		37.9	30.6	
Diuretic	9.8	8.1		29.9	25.8	

BP, blood pressure; RAAS, renin-angiotensin-aldosterone system.
[a] Data are median (interquartile range) and analyzed using the Wilcoxon rank-sum test.
[b] Analyzed using Chi-squared test.

Table 4
Sex-dependent HbA1c values and antidiabetic treatment in primary and secondary prevention.

	Primary prevention			Secondary prevention		
	Women	Men	*p* value	Women	Men	*p* value
n	6,867	7,043		287	787	
HbA1c, %	5.6 (5.3–6.2)	5.7 (5.4–6.6)	<0.001[a]	5.9 (5.5–6.7)	6.0 (5.6–6.8)	0.198[a]
Antidiabetic treatment, %			<0.001[b]			0.903[b]
No treatment	81.5	72.8		61.7	60.0	
Oral antidiabetics	17.6	25.8		36.6	38.9	
Insulin	5.0	7.5		16.0	14.9	

HbA1c, glycated hemoglobin.
[a] Data are median (interquartile range) and analyzed using the Wilcoxon rank-sum test.
[b] Analyzed using Chi-squared test.

prevention in Europe, where primary care settings are particularly important, whereas continental differences on recommendations and organization on how to assess risk and intervene at the population level may exist (i.e., gynecologists or dedicated cardiovascular care facilities may play an important role in certain countries). Third, age-adjustment was crucial to investigate sex differences, since cardiovascular risk differs with age between women and men [5,6]. In fact, we could confirm that there was a greater age-dependent increase in measured values of LDL-C, BP, and HbA1c in women compared to men in primary prevention. The difference was particularly profound for LDL-C levels, which were higher in women than in men older than 50 years, while systolic BP levels were higher only in women older than 70–75 years and HbA1c values remained lower in women during almost the entire observation period.

This study has certain limitations. Given the observational nature of our analyses, we cannot completely exclude residual confounding. On the other hand, observational studies more likely reflect what is achieved in routine primary care compared to randomized clinical trials [35]. Indeed, our analysis was based on an extensive dataset covering almost 60,000 patients from 62 practices, allowing meaningful comparisons particularly for patients in primary prevention ($n = 56{,}694$), whereas results regarding patients in secondary prevention ($n = 2{,}398$) should be interpreted more cautiously. We could neither account for the general practitioners' judgment of individual patients, nor for patients' preferences, nor for discontinuation of treatments due to real or perceived adverse effects. Also, a large proportion of subjects had missing risk factor measurement rates, which may partly be attributable to missing data in the electronic medical records. Considering that current European guidelines recommend cardiovascular risk assessment only every 5 years in individuals without risk factors close to thresholds mandating treatment [7], the presumably low assessment rates may also result from the relatively short 1-year observation period of this study, and should therefore be interpreted with caution. In addition, patients with hypertension often measure their BP at home, and these measurements may not be recorded by general practitioners. However, we did not expect that these limitations introduced a significant bias into the analysis that primarily focuses on sex differences, since they likely apply to both women and men equally. Lastly, even though women may also have their BP measured when seeing a gynecologist, cardiovascular prevention in Switzerland is largely provided in primary care settings, and hence this likely did not introduce a significant bias.

In conclusion, compared to other modifiable cardiovascular risk factors, women in primary care are disproportionally affected by inferior control of LDL-C compared to men independent of their cardiovascular risk. Improvements in awareness, assessment, and therapy of elevated LDL-C may thus be needed to reduce inherent inequalities in prevention of CVD between women and men.

CRediT authorship contribution statement

Yael Rachamin: Conceptualization, Formal analysis, Writing – original draft. **Thomas Grischott:** Writing – review & editing. **Thomas Rosemann:** Resources, Writing – review & editing. **Matthias R. Meyer:** Conceptualization, Writing – original draft, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2021.02.024.

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